REMARKS

Allowed Claims

Applicants' thank the Examiner for indicating the Claims 19-21, 60, 63, 64, 69-76, 81-84, 87 and 88 are allowed.

Paragraph 3. Rejection of Claims 16 and 17 Under 35 U.S.C. § 102(a)

The Examiner has reapplied the rejection of Claims 16 and 17 under 35 U.S.C. § 102(a) as being anticipated by Marchese *et al.* The rejection was originally made in the Office Action dated December 15, 2000 (Paper No. 5), and was withdrawn in the Office Action dated July 25, 2001 (Paper No. 8). The Examiner states that the protein taught by Marchese *et al.* is substantially identical in structure to SEQ ID NO:2, and is presumed to bind IP-10 and Mig and to have the same downstream effects as the protein of SEQ ID NO:2, absent any evidence to the contrary. (Office Action at page 5, lines 1-2, and page 2, lines 18-21.) The Examiner further states that it is not necessary that an inherent property be recognized in order for an invention to be anticipated. (Office Action at page 4, lines 11-12.)

The Examiner acknowledges that the GPR9 amino acid sequence of Marchese *et al.* lacks the four N-terminal amino acids of SEQ ID NO:2. Despite this difference in primary structure, the Examiner concludes that the GPR9 amino acid sequence of Marchese *et al.* is substantially identical to SEQ ID NO:2 and presumes that a protein consisting of the GPR9 amino acid sequence would have the same IP-10 and Mig binding activity as Applicants' CXCR3 protein having the amino acid sequence of SEQ ID NO:2. The Examiner's conclusion is improper, the claims are not anticipated and inherency is not established, because (A) Marchese *et al.* does not enable a protein consisting of the disclosed GPR9 amino acid sequence, and (B) GPR9 is not substantially identical to SEQ ID NO:2.

A claim is anticipated under 35 U.S.C. § 102 only if "each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Brothers Inc. v. Union Oil Company of California, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987) (see also, MPEP § 2131, pp. 2100-70 *et seq.*, Edition 8 (Rev. 1, February 2003)). An anticipating reference must enable one skilled in the art to make the anticipating subject matter.

PPG Industries, Inc. v. Guardian Industries Corp., 37 USPQ2d 1618, 1624 (Fed. Cir. 1996). The reference must place the person of ordinary skill in the art in possession of the anticipating subject matter. In re Spada, 15 USPQ2d 1655, 1657 (Fed. Cir. 1990).

A. MARCHESE *ET AL.* DOES NOT ENABLE A PROTEIN CONSISTING OF THE GPR9 AMINO ACID SEQUENCE.

Marchese *et al.* discloses that the deduced GPR9 amino acid sequence is similar to sequences of known G protein-coupled receptors, in particular the IL-8 receptors. However, Marchese *et al.* contains no teachings or guidance for producing a protein that consists of the GPR9 amino acid sequence. If such a protein could have been produced, the person of ordinary skill in the art at the time the invention was made would have had to supplement the teachings of the reference and/or resort to undue experimentation. Therefore, the reference does not anticipate.

The nucleic acid encoding the deduced amino acid sequence of GPR9 disclosed in Marchese *et al.* does not include an initiator codon. (See Marchese *et al.* at page 337, Figure 1.) It is well-known that an initiator codon is necessary to produce any protein by translation. Thus, a protein consisting of the GPR9 amino acid sequence could not have been produced by expressing the nucleic acid disclosed in Marchese *et al.*

Perhaps the person of ordinary skill in the art at the time the invention was made could have chemically synthesized a polypeptide consisting of the GPR9 amino acid sequence. However, even if this were possible, a polypeptide produced by chemical synthesis would not have had the claimed property of binding IP-10 or Mig, unless the polypeptide were properly folded to form an active receptor protein. Marchese *et al.* does not teach how to fold the GPR9 amino acid sequence, and no reasonable basis has been set forth to conclude, based on Marchese *et al.*, that a synthetic polypeptide could have been properly folded to form a protein having 7-transmembrane spanning domains at the time the invention was made.

Therefore, Marchese *et al.* does not anticipate the claims because it only discloses a conceptual or theoretical amino acid sequence and does not enable the person of ordinary skill in

the art to make a protein consisting of that amino acid sequence that binds IP-10 or Mig without modifying the teachings of Marchese *et al.*

B. GPR9 IS NOT SUBSTANTIALLY IDENTICAL TO SEQ ID NO:2.

The Examiner is of the opinion that the GPR9 amino acid sequence of Marchese *et al.* is substantially identical to SEQ ID NO:2 and presumes that a protein consisting of the GPR9 amino acid sequence would have the same IP-10 and Mig binding activity as Applicants' CXCR3 protein having the amino acid sequence of SEQ ID NO:2. Based on this opinion, the Examiner relies on In re Best and In re Spada to shift the burden to Applicants to prove that the GPR9 disclosed in Marchese *et al.* does not bind IP-10 or Mig. In re Best, 195 USPQ 430 (C.C.P.A. 1997); In re Spada, 15 USPQ2d 1655 (Fed. Cir. 1990). Shifting the burden to Applicants is improper because this case is distinguishable from Best and Spada, and the GPR9 sequence of Marchese *et al.* is not substantially identical the SEQ ID NO:2.

In Best, claims drawn to a process for making a crystaline zeolite aluminosilicate molecular sieve catalyst and to a composition that was the product of the process were rejected as being anticipated by U.S. Patent No. 3,354,077 (Hansford), which disclosed a similar process. In re Best, at 432. The Examiner and the Board found that all limitations of the process claims were expressly disclosed in Hansford except for the rate of cooling, which was expressed functionally in Best's claims. Id. They further found that any sample produced using the method of Hansford would necessarily be cooled, and that it was reasonable to conclude that the cooling in the Hansford method met the functional rate of cooling in Best's claims. Id. Because the claimed compositions were the products of Best's process, they were also rejected as being anticipated by the product of the Hansford process. Id.

On appeal the court affirmed these rejections and articulated the rule that when "claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of the claimed products." Id., at 433.

Similarly, in Spada claims to a pressure sensitive adhesive composition comprising a copolymer made from specified classes of monomers in specified proportion were rejected as being anticipated U.S. Patent No. 3,554,987 (Smith), which disclosed polymerization of the same monomers using the same or similar techniques. In re Spada, at 1656-1657. The court affirmed the Board's holding that the virtual identity of monomers and procedures used to prepare the claimed polymers and those disclosed in Smith, was sufficient to establish a *prima facie* case of unpatentability for lack of novelty. Id. Again, the court stated that when "the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." Id., at 1658.

In both Best and Spada, the prior art disclosed and placed the person of ordinary skill in the art in possession of methods and the products of those methods. Further, in both cases, the prior art methods were identical or substantially identical to the methods used to produce the claimed compositions. Thus, the court concluded that the claimed compositions were identical or substantially identical to the prior art, and shifted the burden of proving that they were not to the applicants. However, shifting the burden to Applicants in this application is improper because, unlike Best and Spada, Marchese *et al.* does not place the person of ordinary skill in the art in possession of a product this is identical or substantially identical to Applicants' invention.

It is improper to conclude that amino acid sequences that differ in the N-terminal extracellular regions are substantially the same and would have the same ligand binding activities, because the sequence of Marchese *et al.* and SEQ ID NO:2 differ in a region implicated in ligand binding activity. At the time the invention was made, the person of ordinary skill in the art knew that the N-terminal extracellular regions of chemoattractant and chemokine receptors were involved in ligand binding. Evidence of the knowledge of the person of ordinary skill in the art at the time the invention was made is provided, for example, at page 16, lines 17-26 of the specification, where Applicants teach:

> Information regarding the structure and function of mammalian G protein coupled receptors, including CXC chemokine and CC chemokine receptors, provides a basis for dividing mammalian CXCR3 proteins into functional domains (Murphy, P.M., "The molecular biology of leukocyte chemoattractant receptors," *Annu. Rev. Immunol., 12*:593-633 (1994) and Gerard, C. and N.P. Gerard, "The pro-inflammatory seven transmembrane

segment receptors of the leukocyte," *Curr. Opin. Immunol.*, *6*:140-145 (1994), and references cited therein).

The cited articles by Murphy (Murphy, P.M., *Annu. Rev. Immunol.*, *12*:593-633 (1994), Reference AR, of record) and Gerard (Gerard, C. and N.P. Gerard, *Curr. Opin. Immunol.*, *6*:140-145 (1994); Reference AS3, of record) describe structural features of leukocyte chemoattractant receptors which are involved in receptor function, including α chemokine receptors, of which CXCR3 is a member. For example, Murphy teaches that the sequence differences between three α chemokine receptors, namely IL8RA, rabIL8R and IL8RB, cluster in the proposed N-terminal segment, the e2 loop and the C-terminus. (Murphy, P.M., at page 613, last paragraph.) Murphy further teaches that N-terminus and e3 loop may represent important domains in ligand binding for the IL8 receptors. (Murphy, P.M., at page 614, first paragraph.) In addition, Murphy discusses the results of studies which investigated ligand binding specificity using chimeric receptors in which the N-terminal segments of IL8RB and rabIL8R were switched. Murphy states that the results of these N-terminal chimeric receptor studies "clearly implicate this [N-terminal] domain in determining the selectivity of the receptors for Groα and NAP-2." (Murphy, P.M., at page 613, last paragraph.)

In agreement with this, Gerard teaches that "[t]he acidic nature of the amino-terminal region of the C5a and chemokine receptor complements the cationic ligands, and forms part of the ligand-binding site." (Gerard, at page 140, column 2, lines 4-7.) Gerard also teaches that the third extracellular loop of the α chemokine receptors, IL-8 receptor A (CXCR1) and IL-8 receptor B (CXCR2), contains structures critical for ligand binding. (Gerard, at page 140, column 2, lines 7-10.)

Murphy and Gerard clearly teach and provide evidence of the importance of the N-terminal domain of α-chemokine receptors in ligand binding, and demonstrate that the person of ordinary skill in the art knew that the N-terminal domain of chemokine receptors (*e.g.*, α-chemokine receptors, such as CXCR3) were involved in ligand binding.

In view of these teachings, which demonstrate the art-known relationship between the N-terminal extracellular region of chemokine receptors and the ligand binding activity and specificity of such receptors, it is improper to conclude that the amino acid sequence disclosed in

Marchese *et al.* is substantially the same as and would necessarily have the same ligand binding properties as SEQ ID NO:2, because the sequence differ in the region implicated in ligand binding activity.

Marchese *et al.* does not anticipate Claims 16 and 17, because it does not support the Examiner's inference that a protein consisting of the GPR9 amino acid sequence would inherently bind IP-10 or Mig. In particular, the reference does not enable the person of ordinary skill in the art at the time the invention was made to produce a protein consisting of the GPR9 amino acid sequence. Moreover, shifting the burden to Applicants to prove that a protein consisting of the GPR9 amino acid sequence does not bind IP-10 or Mig is legally improper, because Marchese *et al.* does not place the person of ordinary skill in the art in possession of a protein that is substantially identical to Applicants' CXCR3 protein having the amino acid sequence of SEQ ID NO:2. Reconsideration and withdrawal of the rejection are respectfully requested.

Paragraph 5. Rejection of Claims 61, 62, 65-68, 77-80, 85 and 86 Under 35 U.S.C. § 103(a)

Claims 61, 62, 65-68, 77-80, 85 and 86 are rejected under 35 U.S.C. § 103(a) as being obvious over Marchese *et al.* in view of Sambrook *et al.* (Molecular Cloning, 2nd. Edition, Cold Spring Harbor Laboratory Press (1989)). The Examiner states that Marchese *et al.* does not teach modifications, such as fusion proteins or detectable labels. The Examiner further states that Sambrook *et al.* teaches such modifications and that it would have been obvious for one of ordinary skill in the art to combine the teachings of Marchese *et al.* and Sambrook *et al.* to produce fusion proteins and detectably labeled proteins.

A finding that the claimed invention is obvious under 35 U.S.C. § 103 requires that (1) "the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process;" and (2) that "the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success." In re Vaeck, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

"Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." Id. (emphasis added).

As discussed in detail above, Marchese *et al.* does not enable the person of skill in the art at the time the invention was made to produce a protein that consists of the GPR9 amino acid sequence, and does not disclose that such a protein would bind a chemokine. The statement in the reference suggesting that future studies will involve binding assays, in the absence of any teachings as to how to produce a GPR9 protein, is insufficient to suggest to the person of skill in the art at the time the invention was made that the claimed fusion proteins should be produced.

In addition, the claims are not obvious because the prior art did not provide a reasonable expectation of success in arriving at the claimed fusion proteins. The rejected claims recite that the fusion protein comprises a CXCR3 protein or variant that binds a chemokine selected from the group consisting of IP-10 and Mig. However, as discussed above, Marchese *et al.* does not teach or provide a basis for inferring that a protein consisting of the GPR9 amino acid sequence would inherently bind IP-10 or Mig. The general teachings of the laboratory manual Sambrook *et al.* contains nothing to cure the deficiency in the teachings of Marchese *et al.* on this point. Accordingly, the rejection is improper. Obviousness cannot be predicated on what is unknown. In re Spormann, 150 USPQ 449, 452 (C.C.P.A. 1966).

Therefore, even if the person of skill in the art were motivated to try to produce a fusion protein that contained the GPR9 amino acid sequence of Marchese *et al.*, he could only have hoped that it might bind some as yet unidentified ligand. Such a hope or wish cannot be equated with the requisite reasonable expectation of success in producing the claimed fusion proteins comprising a CXCR3 protein or variant that binds a chemokine selected from the group consisting of IP-10 and Mig. Reconsideration and withdrawal of the rejection are respectfully requested.

Supplemental Information Disclosure Statements

A Second Supplemental Information Disclosure Statement (SIDS) with Form PTO 1449 citing references AC (U.S. Patent No. 6,140,064) and AD (U.S. Patent No. 6,184,358 B1) was filed on July 23, 2002. Applicants' representatives have not received an initialed copy of that Form PTO 1449 indicating the references AC and AD have been considered by the Examiner. If

the Examiner has not done so already, she is requested to consider the information provided in the SIDS filed July 23, 2002, and to return an initialed copy of the Form PTO 1449 indicating that references AC and AD have been considered with the next Office Communication.

The Examiner is also requested to acknowledge that the information provided in the Third SIDS filed March 24, 2003 has been considered.

CONCLUSION

In view of the above remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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Dated: November 7, 2003